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(57) Abstract

The present invention discloses a novel solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, polyethylene glycol, and propylene glycol. In another aspect, the present invention discloses a pharmaceutical composition comprising the solution of the invention. In another aspect, the present invention discloses a gelatin capsule filled with the composition of the present invention.

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SOLUTIONS CONTAINING AZASTEROIDS

The present invention relates to certain pharmaceutical compositions comprising 4-aza steroids and/or 6-aza steroids. In particular, the present invention relates to solutions comprising a steroid 5-alpha reductase inhibitor.

Pharmaceutically active compounds can be delivered in a variety of forms, for example in a soft elastic gelatin capsule. Methods for preparation of soft gelatin capsules are well known. See, for example, J.P. Stanley, *Soft Gelatin Capsules, Ch. 13 - Part Two in: The Theory and Practice of Industrial Pharmacy*, eds. L. Lachman et. al., 3 rd Ed., pp. 398-412, 1986, and W.R. Ebert, *Soft Elastic Gelatin Capsules: A Unique Dosage Form*, Pharmaceutical Technology, Vol. 1, No. 5.

The choice of excipients is important in order to ensure good solubility and good bioavailability of the pharmaceutically active compound. See for example, A. Matso, *Excipients Commonly Used in Soft Gelatin Capsules: Their Analysis and Usefulness*, Novel Drug Formulation Systems and Delivery Devices International Seminar, pp. 76-81,(1991). K. Hutchison, *Encapsulation in Softgels for Pharmaceutical Advantage*, Spec. Pub. - R. Soc. Chem., Vol. 138, pp 86-97, (1993), M.S. Patel et. al., *Advances in Softgel Formulation Technology*, Manufacturing Chemist, August 1989, and I.R. Berry, *Improving Bioavailability with Soft Gelatin Capsules*, Drug & Cosmetic Industry, pp. 32, 102-108, (September, 1983). Particular issues with respect to formulation of hydrophobic pharmaceutically active compounds has been described, for example in K. Hutchison, *Formulation of Softgels For Improved Oral Delivery of Hydrophobic Drugs*, Spc. Pub. - R. Soc. Chem., Vol. 161, pp 133-147 (1995).

Liquid filled hard gelatin capsules have also been utilized. See, for example, D. Cade et. al., *Liquid Filled and Sealed Hard Gelatin Capsules*, Drug Development and Industrial Pharmacy, 12(11-13): 2289-2300, (1986).

Aza steroids are an important class of pharmaceutically active compounds. In particular there are 4-aza steroids and 6-aza steroids known to be inhibitors of

the enzyme testosterone 5-alpha-reductase (hereinafter "5AR inhibitors"). Such compounds are thought to be useful in the treatment of benign prostatic hyperplasia, prostate cancer and other diseases. See, for example, U.S. Pat. Nos. 4,377,584 (Rasmusson et al.), 4,220,775 (Rasmusson et al.), 4,732,897 (Cainelli et al.) 4,760,071 (Rasmusson), 4,845,104 (Carlin et al.), 4,859,681 (Rasmusson), 5,302,589 (Frye et al.), 5,438,061 (Bergman et al.), 5,543,406 (Andrews et al.), 5,565,467 (Batchelor et al.), and WO 95/07926 (Batchelor et al.). One such 5AR inhibitor, finasteride, is commercially available from Merck & Co., Inc. as PROSCAR™. These pharmaceutically active compounds are not easy to dissolve. These solubility challenges can affect bioavailability possibly resulting in reduced or unpredictable bioavailability.

Briefly, in one aspect, the present invention discloses a novel solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, polyethylene glycol (PEG), and propylene glycol (PG).

In another aspect, the present invention discloses a pharmaceutical composition comprising the solution of this invention. The composition of this invention is particularly suitable for use as a fill formulation for gelatin capsules.

In another aspect, the present invention discloses a gelatin capsule filled with the composition of the present invention.

The composition of this invention has improved bioavailability over standard tablets or suspensions.

Some of the steroids useful in this invention are potent teratogens. Converting the steroid from a free powder to a solution early in the manufacturing process provides a safer process. There is less risk in working with the solution than with the free solid.

Also, some of these steroids are prone to oxidation. Gelatin capsule formulations can be much more resistant to oxidation due to the low oxygen permeation of typical gelatin shells. See, for example, F.S. Hom et al., *Soft Gelatin*

capsules II: Oxygen Permeability Study of Capsule Shells, J. Pharm. Sci., Vol. 64 (No. 5), pp 851-887 (1975).

Given the PEG content of the compositions of this invention, the compositions of this invention have surprisingly short drying time. This surprisingly short drying time is beneficial for manufacturing because this shortens the time from manufacturing to packaging and shipping, thereby lowering manufacturing cost.

The aza steroids useful in this invention can be any pharmaceutically active aza steroid or pharmaceutically acceptable solvate thereof. Preferred classes of aza steroids are the 4-azasteroid class of 5-alpha reductase inhibitors (5AR inhibitors) and the 6-aza class of 5-alpha reductase inhibitors. For example, any of the 5AR inhibitors disclosed in the above cited patents. Particularly preferred aza steroids are the 4-aza steroids. Particularly preferred 4-aza steroids include finasteride, 17-beta-N-(2,5,-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one which is the steroid is that disclosed in U.S. Pat. No. 5,565,467 (Batchelor et al.), and 17-beta-N-1-(3,4-methylenedioxy-phenyl)-cyclohexylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one and 17-beta-N-(1-(p-chlorophenyl))-cyclopentylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one which are both disclosed in WO 95/07926 (Batchelor et al.). These steroids can be prepared by well-known methods, for example as described in the above cited patents.

The aza steroid is preferably present in the range of from 0.00075 to 0.4% by weight of the solution of this invention, more preferably from 0.0075 to 0.3 % by weight of the solution of this invention.

The PEG useful in this invention preferably has an average molecular weight range of 200-600, at which PEG is in liquid state. Particularly preferred is PEG with an average molecular weight of around 400 (PEG 400). Preferably, the PEG is at least 90% by weight of the solution of this invention.

The PG is preferably from 1 to 7.5% by weight of the solution of this invention, more preferably from 4 to 6% by weight of the solution.

Generally it is preferable to include in the composition a surfactant. Suitable surfactants include, polyoxyethylene(20)sorbitan monooleate (Polysorbate 80), sodium dodecyl sulfate, and dioctylsulfosuccinate sodium salt (Docusate sodium). Surfactants may be used alone or in combination. A particularly preferred surfactant is Polysorbate 80. The surfactant or surfactant mixture is preferably from 0.05 to 1.0% by weight of the composition of this invention.

It may also be useful to include an anti-oxidant in the composition. Suitable anti-oxidants include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ascorbic acid. A particularly preferred anti-oxidant is butylated hydroxytoluene. Antioxidants may be used alone or in combination. The antioxidant or mixture of antioxidants is preferably from 0.001 to 0.5% by weight of the composition of this invention.

The pharmaceutical composition of the present invention is particularly useful as a fill formulation for gelatin capsules, most preferably soft gelatin capsules.

Experimental

In the following experiments, a pharmaceutically active 4-aza steroid was utilized in various solubility studies. The pharmaceutically active steroid utilized was 17-beta-N-(2,5,-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-ene-3-one. This steroid is described in the '467 patent and can be prepared by known methods including the methods described in the '467 patent.

The solubility of the steroid was determined by suspending excess amount of the steroid in about 1 mL of various aqueous and organic media. The resulting suspension was tumbled in a Vankel® rotating water bath maintained at 25°C and protected from light. At the end of an equilibration time, usually between 1 and 12 days, excess solid was removed by filtercentrifugation through 0.22μ filters. The resulting supernatant was then assayed for steroid concentration against an external standard. The concentration of steroid in the supernatant was determined by HPLC

analyses using a Hewlett Packard 1090 Series II/M with a DOS Chem Station. The HPLC conditions are summarized below in Table 1. The results of the solubility in various aqueous media is summarized in Table 2, and in various organic media is summarized in Table 3. Table 4 summarizes the solubility in various compositions containing a complexing agent (2-hydroxypropyl-beta-cyclodextrin). Table 5 summarizes the solubility in various oils. In the following Tables and experiments, Mili Q™ plus water is a reverse osmosis water, THF is tetrahydrofuran, DMSO is dimthylsulfoxide, Labrafil™ is a mixture of unsaturated polyglycolyzed gylcerides obtained by partial alcoholysis of corn oil or apricot kernel oil, consisting of glycerides and polyethylene glycol esters, SDS is sodium dodecyl sulfate, "model duodenum bile salts" is a mixture of sodium glycocholate, sodium glycochenodesoxycholate, sodium glycodesoxycholate, sodium taurocholate, sodium taurochenodesoxycholate, sodium taurodesoxycholate, sodium chloride, lecithin, and phosphate buffer, Tween 80 is polyoxyethylene(20)sorbitan monooleate, the PEG 400 was purchased from Union Carbide, Molescusol™ is 2-hydroxypropyl-beta-cyclodextrin, and Intralipid™ is a mixture of soy bean oil, phospholipids, glycerin USP, and water for injection. Unless stated otherwise, all % are by weight, for example, "v/v" means % by volume.

Table 1. HPLC Conditions

Column	250 x 4.6 mm Zorbax Rx C18
Mobile Phase	A. 0.1% v/v TFA B. 0.05% v/v TFA in Acetonitrile
Percent Composition	40%B-95%B in 20 minutes (10 min hold)
Flow rate	1.0 mL/minute
Detection wavelength	210/240
Oven Temperature	35°C

Table 2. Solubility in Aqueous Media

Medium	Concentration (mg/mL)
Milli Q® plus water	< 0.0039
0.1N HCl	< 0.0039
0.5% carboxy methylcellulose	< 0.0039
1% Labrafil®	highly degraded
0.02% SDS	< 0.0039
0.01% docusate sodium	< 0.0039
0.1% Tween 80	< 0.0039
0.1% Tween 80, 0.02% SDS	< 0.0039
Model duodenum bile salts	0.0386

Table 3. Solubility in Organic Media

Medium	Concentration (mg/mL)
Propylene glycol	6.21
Polyethylene glycol 400	3.27
PEG 400, 0.1% Tween 80	3.91
Propylene carbonate	6.24
Ethyl acetate	14.49
THF	225.44
Acetonitrile	7.44
Acetone	46.97
DMSO	130.40
Benzyl Alcohol	>34
Ethanol	45.59
70% aqueous ethanol	2.73
Isopropanol	29.98

Table 4. Solubility in 2-Hydroxypropyl-β-cyclodextrin Solutions

Medium	Concentration (mg/mL)
10% Molecusol®	0.03
20% Molecusol®	0.12
40% Molecusol®	0.79
40% Molecusol®/25% PEG400/5%PG	0.08
40% Molecusol®/50% aqueous PEG 400	0.56

Table 5. Solubility in Various Oil Base Systems

Medium	Concentration (mg/mL)
Sesame oil	0.52
Safflower oil	0.39
Soybean oil	0.44
Cottonseed oil	0.53
Corn oil	0.56
Castor oil	2.01
Olive oil	0.44
Peanut oil	0.46
Mineral oil	0.007
1% Span 20/cotton seed oil	0.62
10% benzyl alcohol/cottonseed oil	2.77
Intralipid® 20%	0.009

The solubility data show that these types of steroids are very difficult to dissolve. In addition, if the dissolved steroid is going to be used in a gelatin capsule, the choice of excipients needs to be acceptable excipients for use with gelatin capsule systems. Therefore, the following excipients were considered viable components for this formulation:

Ethanol

Propylene glycol

Polysorbate 80

Polyethylene glycol 400

These excipients were then further evaluated in order to discover the best formulation. The experiment was conducted using a mixture of the following components at the corresponding percentages:

Ethanol	0%, 5%, and 10%
Propylene glycol	5%, 6.25%, and 7.5%
Polysorbate 80 (Tween 80)	0%, 0.05%, and 0.1%
Polyethylene glycol 400	QS

A designed experiment was then performed following the experimental design summarized in Table 6.

Table 6. Experimental Parameters

Run #	Ethanol (%)	PG (%)	Tween 80 (%)	PEG 400 (%)
1	10	5	0.1	84.9
2	10	7.5	0.1	82.4
3	10	5	0	85
4	5	7.5	0.05	87.45
5	10	7.5	0	82.5
6	10	5	0	85
7	0	7.5	0.1	92.4
8	0	7.5	0	92.5
9	10	7.5	0.1	82.4
10	0	6.25	0.05	93.7
11	5	6.25	0.1	88.65
12	0	5	0.1	94.9
13	0	6.25	0.05	93.7
14	0	5	0	95

The experimental design included 14 runs which resulted in a full quadratic equation and error detection. JMP® was used to fit the data. The solubility of the steroid in the various compositions of the designed experiment were evaluated as described above. The results are summarized in Table 7.

Table 7. Solubility Results

Run #	Solubility (mg/mL)
1	5.95
2	5.82
3	4.84
4	4.21
5	4.57
6	3.26
7	3.65
8	3.97
9	5.42
10	3.92
11	3.80
12	3.90
13	0.87
14	3.14

The data from the designed experiment show that increasing the concentration of ethanol and polysorbate 80 increased the solubility of the steroid. It also indicated that propylene glycol does not have a significant effect on the solubility at the studied concentrations.

The preferred compositions were then used to prepare fill formulations suitable for use in gelatin capsules. For manufacture of 0.1, 0.5, and 2.5 mg soft-gelatin capsules, propylene glycol USP was heated to 35-50°C. Then butylated

Hydroxytoluene NF is added and the mixture is stirred until dissolved. To the resulting solution was added Polyethylene glycol 400 NF and mixed. Polysorbate 80 NF was then added and mixed. Then the steroid was added and mixed, heating to 40-45°C if necessary, until dissolved. The solution was deaerated prior to encapsulation.

The gelatin was prepared by blending gelatin NF, glycerin USP, and purified water USP. The resulting mixture was heated in a pressurized reactor to melt the gelatin. The gelatin was then maintained in the molten state until used for encapsulation.

Encapsulation was performed using a rotary die process. The heated gelatin was fed to an encapsulation machine where it entered two spreader boxes which cast the gelatin on a cooling drum, thus forming two gelatin ribbons. Each gelatin ribbon was lubricated with Fractionated Coconut Oil on the internal side and Fractionated Coconut Oil with 0.1% Lecithin NF on the external side. The Fractionated Coconut Oil prevents the gelatin from sticking to equipment and the Lecithin NF prevents the capsules from sticking together after manufacture, prior to drying. The ribbons were then conveyed to the encapsulation roller. Die cavities to form the capsules are located on the circumference of the two adjacent rollers, which rotate and pull the gelatin ribbons between them. The fill solution was injected, by a metered positive-displacement pump, between the gelatin ribbons forcing them to expand and fill the die cavities. As the capsules were filled, they were simultaneously shaped, sealed and cut from the gelatin ribbon by the encapsulation rollers. The capsules were then conveyed to the rotating basket dryer.

The capsules were dried by tumbling in a rotating basket dryer to remove sufficient moisture to allow handling. They were then transferred onto trays and allowed to dry until the moisture level of the fill solution was not more than 8% (w/w). Drying time is the time required to reach the 8% moisture level.

Batches were prepared containing 0.1, 0.5, and 2.5 mg per capsule. The compositions are summarized in Table 8.

Table 8. 0.1, 0.5, and 2.5 mg compositions

Component		Quantity per batch (kg)		
Capsule Strength (steroid mg)		0.1	0.5	2.5
Steroid		0.0006	0.003	0.015
Polyethylene Glycol 400	NF	7.420082	7.39842	7.38642
Propylene Glycol	USP	0.390	0.390	0.390
Polysorbate 80	NF	0.0078	0.0078	0.0078
Butylated Hydroxytoluene	NF	0.00078	0.00078	0.00078
Total Fill Solution per batch (kg)		7.8	7.8	7.8

The batches were then evaluated for drying times. The drying time for all of the PEG based compositions that were tested was only 1 day. Those skilled in the art will generally expect that soft gelatin capsules containing oil based (hydrophobic) fill material to have drying times of about 3 days, and that PEG based fill materials typically increase drying time compared to oil based compositions. Therefore, the shorter drying time of the PEG based formulation of steroid offers an advantage over typical PEG based formulations, as well as typical oil based formulations.

Those trained in the art will also recognize that although inclusion of propylene glycol in the formulation typically decreases water migration into the fill, propylene glycol typically has no significant effect on drying time. In our case however, propylene glycol results in a greater than expected decrease in drying time.

These compositions were also evaluated for relative bioavailability using standard methods. Volunteers were randomized to receive drug in either an oral solution of the present invention, a soft gelatin capsule of the present invention, or in a standard tablet. Plasma samples were collected and pharmaco kinetic parameters (AUC, C_{max}, T_{max}) were compared between the treatment groups. The relative

bioavailability from the solution and soft gelatin capsule of the present invention was 80% to 90% compared to 10% to 20% for the same amount of steroid in a tablet.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein and may include, by way of example and without limitation, one or more of the following claims.

Claims

What is claimed is:

1. A solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, polyethylene glycol, and propylene glycol.

2. The solution of Claim 1 wherein said steroid is a 4-aza or a 6-aza steroid.

3. The solution of Claim 2 wherein said steroid is a 17-beta-substituted carbonyl-4-azaandrost-1-en-3-one or a 17-beta-substituted carbonyl-6-azaandrost-4-en-3-one.

4. The solution of Claim 3 wherein said steroid is a 17-beta-substituted carbonyl-4-azaandrost-1-en-3-one.

5. The solution of Claim 4 wherein said steroid is 17-beta-N-(t-butyl)- carbamoyl-4-aza-5-alpha-androst-1-en-3-one, 17-beta-N-(2,5,-bis-(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one, 17-beta-N-1-(3,4-methylenedioxy-phenyl)-cyclohexylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one, or 17-beta-N-(1-(p-chlorophenyl))cyclopentylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one.

6. The solution of Claim 5 wherein said steroid is 17-beta-N-(2,5,-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one.

7. The solution of any of claims 1 - 6 wherein said steroid is from 0.00075 % to 0.4 % by weight of said solution.

8. The solution of claim 7 wherein said steroid is from 0.0075 % to 0.3 % by weight of said solution.

9. The solution of any of claims 1 - 8 wherein said polyethylene glycol is at least 90 % by weight of said solution.

10. The solution of any of claims 1 - 9 wherein said polyethylene glycol has an average molecular weight of from 200 to 600.

11. The solution of any of claims 1 - 10 wherein said propylene glycol is from 1 % to 7.5 % by weight of said solution.

12. The solution of claim 11 wherein said propylene glycol is from 4 % to 6 % by weight of said solution.

13. A pharmaceutical composition comprising the solution according to any preceding claim.

14. The composition of claim 13 further comprising a surfactant.

15. The composition of claim 14 wherein said surfactant is polysorbate 80, sodium dodecyl sulfate, docusate sodium, or mixtures thereof.

16. The composition of claim 14 or 15 wherein said surfactant is from 0.05 % to 1.0 % by weight of said composition.

17. The composition of any of claims 13 - 16 further comprising an antioxidant.

18. The composition of claim 17 wherein said antioxidant is butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid, or mixtures thereof.

19. The composition of claim 17 or 18 wherein said antioxidant is from 0.001 % to 0.5 % by weight of said composition.

20. A liquid filled gelatin capsule comprising the composition according to any of claims 13 - 19.

21. The gelatin capsule of claim 20 wherein said capsule is a soft gelatin capsule.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/05192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/58 A61K9/08 A61K47/10 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 07926 A (GLAXO) 23 March 1995 cited in the application see claims 1,18,19,23-31 see page 23, line 26 - page 25, line 19 see example 58D ---	1-21
A	WO 97 11702 A (MERCK) 3 April 1997 see claims see page 12, line 29 - page 14, line 20 ---	1-21
A	WO 92 00010 A (SMITHKLINE BEECHAM) 9 January 1992 see claims 1,10,17,19 see example III ---	1-21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 March 1999	11/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

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PCT/EP 98/05192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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